REMARKS

Claims 1-3, 5-11, 22-24 and 26 are pending in this application; Claims 1, 6, 9, and 22 have been amended and claims 4, 12-21 and 25 are cancelled.

The claims have been amended to more precisely define the types of gaseous fluids that may be used, support being found in the paragraph bridging pages 11 and 12 in the application as filed. Claim 1 has also been amended to incorporate dependent claim 4, and claim 22 has also been amended to incorporate dependent claim 25, to specify repeated processing; claims 4 and 25 have been cancelled. There being no new matter, entry of these amendments is respectfully requested.

I. Telephonic Interview

Applicants gratefully acknowledge and appreciate the telephonic interview held with Examiner Kumar on June 3, 2004, to discuss the merits of this application. The interview was very helpful in clarifying the Examiner's position and advancing the prosecution of this application.

During the interview, the rejections under 35 USC 112 and 35 USC 103 were discussed. Regarding the 35 USC 112, first paragraph, rejections, Applicants argued that one skilled in the art would be enabled to practice the full scope of the claimed invention based on the teachings in the specification and knowledge in the art. In response, the Examiner requested that: 1) the claims be amended to specifically recite the types of gaseous fluids to be used; and 2) an explanation be provided regarding how to select appropriate solvents and gaseous fluids for any particular solute material, with 3 to 4 examples of how to practice the invention with particular solutes. Regarding the 35 USC 103 rejection, Applicants pointed out the differences between the process of the present invention and the processes disclosed in the cited references. In response, the Examiner requested that: 1) Applicants should more clearly explain the differences between the present invention process and the processes of the cited references; and 2) Applicants should discuss the advantages of the present invention process vs. the processes of the cited references.

Applicants have carefully taken the Examiner's suggestions into consideration prior to filing the present Amendment.

II. Restriction Requirement

The Examiner has restricted the claims of the present application as follows:

Group I. Claims 1-11, 22-26, drawn to a process of preparing a drug compound;

Group II. Claims 12-17, drawn to a method of coating;

Group III. Claims 18-21, drawn to a cleaning method.

In response, Application herein affirm the previous election of Group I with traverse and have cancelled the non-elected claims 12-21, reserving the right to file one or more divisional applications directed to the non-elected subject matter.

III. Rejections Under 35 USC 112

Claims 1-11 and 22-26 stand rejected under 35 USC 112, first paragraph, for failing to comply with the enablement requirement. Examiner argues that the specification is not enabling to make and use the invention commensurate in scope with the claims, particularly in reference to the use of various solutes, solvents and gaseous fluids in the process of the present invention.

Applicants respectfully disagree and submit that a person of ordinary skill in this art would be readily enabled to practice the present processes without undue experimentation upon reading the present specification and in light of the existing knowledge in the art.

At the outset, Applicants point out that they have amended the claims to specifically recite the types of gaseous fluids to be used in the claimed processes, as specifically requested by the Examiner at the interview.

All the processes of the present invention involve the dissolution of a gaseous fluid into a solution (i.e., a solvent containing dissolved solute material) to a level sufficient to precipitate out the solute material from the solution. The dissolution of the gaseous fluid into the

solution causes expansion of the solution and subsequent conversion of the solution from acting as a solvent for the solute to being an antisolvent for the solute, resulting in solute precipitation. This procedure is possible by selection of a solvent and gaseous fluid combination such that the solute material to be precipitated has a higher solubility in the solvent than in the gaseous fluid, and the gaseous fluid is at least partially soluble in the solvent. These characteristics become clear upon reading the present specification, esp. pages 10-13, which clearly highlights the broad scope of possible solute/solvent/gaseous fluid combinations that may be employed within the context of the processes of the present invention when these parameters are followed. For a detailed discussion regarding the selection of appropriate solvent/gaseous fluid combinations for a particular solute, please see the present specification at:

- Solute – page 11, lines 9-12
- Solvent – page 12, lines 5-12
- Gaseous fluid – page 4, line 19- page 5, line 8; and page 11, line 22 to page 12, line 4.

Moreover, a patent application must always be read in light of the state of the art existing at the time the application was filed in order to determine whether a particular disclosure is enabling. See MPEP 2164.05(a) and cases cited therein.

The process of the present invention is a novel, improved Gas-Antisolvent (GAS)-type process for solute precipitation involving the dissolution of a gaseous fluid antisolvent into a solution containing a dissolved solute material to a level sufficient to precipitate out the solute material from the solution. GAS-type processes have been in use for over a decade. See, e.g., Gallagher *et al.*, *Gas Antisolvent Recrystallization: New Process To Recrystallize Compounds Insoluble in Supercritical Fluids*, Ch. 22, American Chemical Society Symposium Series, No. 406 (1989), and Krukonis *et al.*, US Patent No. 5,360,478. Gallagher and Krukonis report the exploitation of the ability of gaseous CO_2 to dissolve in organic solvents to crystallize CO_2-insoluble nitroguanadine and cyclotrimethylene-trinitramine (RDX), respectively, from an organic solution. The GAS process has become accepted as a standard method for particle precipitation. In the last several years, multiple research groups have published reviews describing how to use the GAS process to produce particles of gas-

insoluble solutes and disclosing research on parameters that affect the size of particles, their recovery, residual solvents, and methods for continuous manufacture. For instance, see Warwick, B, et al., *Ind. Eng. Chem. Res.*, 2000, 39, pp. 4571-4579, and references 1-9 cited therein, which report on GAS research performed from 1989 to 1999. See also Thiering et al., *J. Chem. Technol. Biotechnol.* 75 (2000), pp. 29-41, 42-53, reporting on use of the GAS process for protein precipitation. Hence, the GAS process is well known in the art and anyone skilled in this art could easily select an appropriate solvent/gaseous fluid combination to achieve the desired precipitation of any particular solute material using this type of process.

The process of the present invention can be practiced with any solvent/gaseous fluid antisolvent system as long as the solvent and gaseous fluid are at least partially miscible and the solute is more soluble in the solvent than in the gaseous fluid antisolvent. Examples of materials that may be precipitated using the processes of the present invention are numerous, including the examples listed in Tables 3 and 4 in Bustami, R.T. et al;, KONA, No. 19, 2001, pp. 57-70. Examples of numerous solvents that can be used as gaseous fluids are given in Table 1 in Bustami. Examples of solvents that may be used for particular solute materials are given in Tables 3 and 4.

Applicants also refer to the following additional U.S. Patents directed to GAS processes for solute precipitation:

- US Patent 5,389,263, Gallagher et al (2/14/1995)
- US Patent 5,864,923, Rouanet et al (2/2/1999)

In view of the foregoing, Applicants respectfully submit that one skilled in the art would readily be able to select appropriate solvents and gaseous fluids for any particular solute material to be precipitated based on the guidance in the application as filed together with the existing extensive knowledge in the art regarding GAS-type processing for solute precipitation, as evidenced by the references cited hereinabove. Accordingly, one skilled in the art would be enabled to practice the present processes without undue experimentation upon reading the present specification in light of the existing knowledge in the art and

withdrawal of these rejections under 35 USC 112, first paragraph, is therefore believed to be in order and is respectfully requested.

IV. Rejection Under 35 USC 103

Claims 1-11 and 22-26 stand rejected under 35 USC 103 over the combination of Hanna (US 6,063,138) in view of Smith (US4,582,731).

A. A person skilled in the art would not have combined the teachings of the cited references in any matter, and there exists no teaching, suggestion or motivation to make such combination:

Hanna describes a Supercritical Antisolvent (SAS) process for material precipitation involving the co-introduction of a solution of the material and a supercritical fluid (SCF) into a particle formation vessel, resulting in extraction of the solvent into the supercritical fluid and precipitation of the material. By contrast, Smith describes an entirely different Rapid Expansion of Supercritical Solutions (RESS) process involving the dissolution of a material into a high-pressure SCF and then rapidly expanding the pressurized SCF solution into a low pressure region to cause precipitation of the material. Thus, the SAS process of Hanna uses supercritical fluid to extract solvent and cause precipitation of a SCF-insoluble material out of a solution, whereas the RESS process of Smith involves the expansion of a SCF solution to cause precipitation of a SCF-soluble material out of the SCF solution containing the material. As these are fundamentally different processes, Applicants submit that one skilled in the art would not have combined such teachings in any manner and there exists no suggestion or motivation for doing so.

B. The combination of references cited would not result in the presently claimed invention:

As discussed previously, the process of the present invention is a novel, improved Gas-Antisolvent (GAS)-type process for solute precipitation involving the dissolution of a gaseous fluid into a solution to a concentration level sufficient to cause precipitation of a

solute material out of the solution. When the amount of gaseous fluid dissolved into the solution reaches a certain concentration level, the expanded solution changes from being a solvent for the solute material to being an antisolvent, and the solute material then precipitates. After precipitation, the pressure is reduced to expel the gaseous fluid and the resulting contracted solvent solution is then recycled and the process repeated on the contracted solution.

Neither Hanna nor Smith, alone or in combination, teach or suggest such steps. Hanna describes a type of Aerosol Solvent Extraction System (ASES) process involving the co-introduction of a solution or suspension of material and a supercritical fluid into a particle formation vessel, resulting in substantially immediate extraction of the solvent into the supercritical fluid and precipitation of the material. Smith describes a Rapid Expansion of Supercritical Solutions (RESS)-type process involving the dissolution of a SCF-soluble material into a high-pressure SCF and then rapidly expanding the pressurized SCF solution into a low pressure region to cause precipitation of the material. Neither reference teaches or suggest the steps of the processes of the present invention.

For ease of reference, the significant differences between the Hanna and Smith processes and the processes of the present invention can be summarized as follows:

FEATURES ↓	**Hanna, US 6,063,138**	**Smith, US 4,582,731**	**Present Invention**
Generic Type →	ASES	RESS	Improved GAS
Purpose: To precipitate →	Material substantially insoluble in SCF	Material substantially soluble in SCF; see col 2/li 20-21	Material substantially insoluble in gaseous fluid/SCF
General Method →	Co-introduction of a solution or suspension of the material in a 1st vehicle, a 2nd vehicle, and a SCF into particle formation vessel; see col 3/li 55-67	Dissolution of material into high pressure SCF followed by rapid expansion of SCF solution into low pressure region; see col 2/li 6-11	Gradual dissolution of gaseous/SC fluid into a solution of the material causing expansion of solution and precipitation
Conditions →	Supercritical conditions ideally maintained in particle formation vessel at all times; fluid mixture in	SC solution rapidly expanded through orifice into low pressure region, resulting in	Dynamic pressure modulation process; cyclical modulations of pressure in particle formation vessel; fluid

	single supercritical state in vessel; see col 5/li 56-58	precipitation; see col 2/li 6-18; col 7/li 25-31	mixture in liquid/vapor equilibrium state in vessel
Nozzle Used →	Yes; col 8/li 23 to col 9/li 54	Yes; col 7/li 48-65; Figs 4 to 6	No
Results →	Simultaneous and immediate extraction of vehicles by SCF and particle formation upon introduction of solution into SCF-filled particle formation vessel; col 1/li 62-67; col. 5/li 53-55; col. 6/li 13-16	Immediate particle formation upon rapid expansion of SCF through orifice; see 2/li 6-18; Figs 4 and 6	Gradual particle precipitation only after dissolution of gaseous/SC fluid into solution to a sufficient concentration level
In-situ solvent recycling	No	No	Yes
Conservation of solvent important	No	No	Yes

As can be seem from the above chart, the process of the present invention and the processes of the cited prior art differ in many respects, including: purpose, general method, use of nozzle, conditions in particle formation vessel, results, in-situ solvent recycling and conservation of solvent. These last two items constitute significant advantages of the present invention process which are not contemplated or possible with the reference processes. These advantages of the present invention, as well as others, are detailed in the specification at page 5, line 21 to page 7, line 2, and page 9, lines 1-11.

In addition, Applicants refer to the following references which discuss the RESS, ASES and GAS as distinct processes, further highlighting recognition in the art that such processes are considered separate and distinct methods of particle precipitation:

1. Bustami, R.T. et al;, KONA, No. 19, 2001, pp. 57-70.
2. Warwick, B, et al., *Ind. Eng. Chem. Res.*, 2002, *41*, pp. 1993-2004
3. Thiering, R. et al, *J. of Supercritical Fluids*, 21 (2001), pp. 159-177 (see Figs 2a-2b)

In view of the above, Applicants have clearly demonstrated that one skilled in the art would not have combined the teachings of the cited references as suggested by the Examiner and, even if they were combined, the combined teachings would not have resulted in the presently

claimed invention. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

V. IDS

Information Disclosure Statements were filed in this application on 6/29/2001 and 7/11/2001 (copies enclosed). The Examiner is respectfully requested to return initialed and signed IDS forms confirming that the cited references have been considered by the Examiner.

In view of the above amendments and remarks, Applicants respectfully submit that this application is now in condition for allowance and earnestly request such action.

If any points remain at issue which can best be resolved by way of a telephonic or personal interview, the Examiner is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

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